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Enantioselective, Stereodivergent Hydroazidation and Hydroamination of Allenes Catalyzed by Acyclic Diaminocarbene (ADC) Gold(I) Complexes

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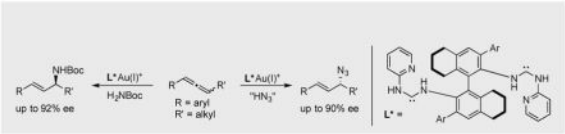
Abstract

The gold-catalyzed enantioselective hydroazidation and hydroamination reactions of allenes are presented herein. ADC gold(I) catalysts derived from BINAM were critical for achieving high levels of enantioselectivity in both transformations. The sense of enantioinduction is reversed for the two different nucleophiles, allowing access to both enantiomers of the corresponding allylic amines using the same catalyst enantiomer.

Graphical Abstract



Chiral allylic azides and amines may be obtained by enantioselective hydroazidation and hydroamination of allenes catalyzed by acyclic diaminocarbene gold(I) catalysts derived from BINAM. The sense of enantioinduction is reversed for the two different nucleophiles, allowing easy access to both enantiomers with a single catalyst enantiomer.

Keywords

hydroazidation; hydroamination; enantioselective; gold catalysis; acyclic diaminocarbene

Allylic amines are an important functional motif in synthetic organic chemistry and they have been utilized in the synthesis of numerous biologically active compounds.[1] Closely related allylic azides are valuable precursors for allylic amines, as well as for amino acids[2]

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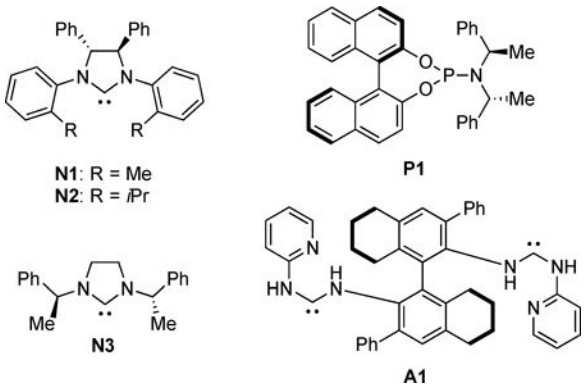
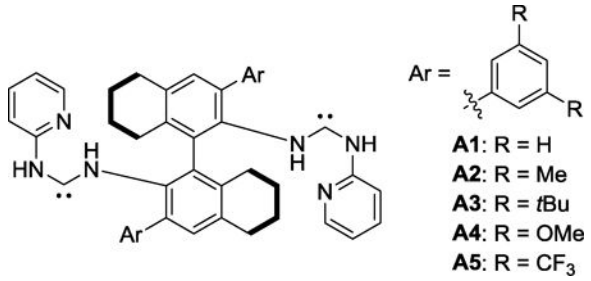
and amine-containing natural products.[3] Allylic azides have typically been prepared via substitution reactions from the corresponding allylic halides, (homo)allylic alcohols, and their derivatives.[4] More recently, Pd-catalyzed C-H activation,[5] and Au-catalyzed hydroazidation of allenes[6] have been employed.

While reports of the synthesis of allylic azides are numerous, methods for asymmetric azidation are few.[7] Fewer still are enantioselective hydroazidation reactions, which have only been reported in a formal sense *via* conjugate addition to activated double bonds (Scheme 1).[8–10] In light of recent examples of transition-metal catalysed asymmetric additions of nitrogen nucleophiles to allenes[11] and the growing utility of organic azides, we sought to develop a gold(I)-catalyzed enantioselective hydroazidation of allenes. Cognizant of potential regioselectivity issues from the Winstein rearrangement[12] of the product allylic azides, we initiated our studies using aryl allene **3a**.[13]



Initial studies revealed that the use of ethereal solvents was critical to obtaining reproducible data.[14] With the choice of solvent established, the enantioinduction afforded by a number of chiral gold(I) catalysts was evaluated under conditions similar to those previously reported, with trifluoroacetic acid (TFA) and trimethylsilyl azide ($TMSN_3$) used for *in situ* generation of hydrazoic acid (Table 2).[6] Traditional chiral phosphine gold(I) catalysts failed to afford high levels of enantioinduction (entries 1,2) as did a previously reported[15] phosphoramidite catalyst (entry 3). Chiral NHC gold(I) catalysts[16] (entries 4–6) also were found to be unsatisfactory. However, the use of a BINAM-derived ADC gold(I) catalyst (entry 7) offered the first encouraging data, and this scaffold established the basis for further exploration.

ADC frameworks are a relatively recent entry into the library of ligands for gold(I) catalysis[17] and their modular, convergent syntheses from amines and gold isocyanides makes them an attractive platform for developing chiral ligands. Applications of ADC gold(I) complexes to asymmetric catalysis have been reported previously by the Slaughter group, the Espinet group, and our own group.[18] As in our previous work, our choice of BINAM as the source of chiral information was motivated by its commercial availability, and the facile introduction of 3,3′-aryl substituents to tune the chiral environment around the metal center. Preliminary results indicated that the ligands with both unsaturated and saturated backbones performed with comparable efficiency; therefore, the latter were chosen due to ease of synthesis[19] and superior crystallization properties.



A number of ADC catalysts were synthesized and evaluated (Table 3). We explored the effect of various 3,3′-aryl substituents on the BINAM scaffold, and found that installation of 3,5-dimethyl (**A2**) or 3,5-bis(trifluoromethyl) (**A5**) aryl groups at these positions gave improved ee's (entries 2 and 5). Further studies were performed with **A5**•$(AuCl)_2$ as the optimal precatalyst, and a crystal structure of the compound was obtained (See Supporting Information).

We hypothesized that the low yields could be the result of catalyst decomposition, as a strong acid (TFA) could disrupt the catalyst's stabilizing intramolecular hydrogen-bonding. On the basis of this hypothesis, we envisioned that a weaker acid in combination with $TMSN_3$ might afford our desired product in greater yield. We tried acetic acid, which is roughly as acidic as hydrazoic acid,[20] and found the results mostly unchanged (compare entries 5 and 6). On the other hand, when water[21] was employed, a substantial increase in the yield was noted (entry 7). Gratifyingly, the formation of the allylic alcohol from hydration of the allene was not observed.[22] Finally, the yields were raised to the desired levels by addition of toluene or chloroform as co-solvents (entries 8 and 9), and the enantioselectivities were elevated by decreasing the temperature and extending the reaction times to compensate for the slower rate of conversion (entry 10).

Encouraged by the results of these optimization efforts, we were eager to investigate whether ADC gold(I) catalysts would be compatible with other nitrogen nucleophiles. We surveyed *tert*-butyl carbamate, *tert*-butyl carbazate, and aniline (Table 3); in all cases, the opposite enantiomer of the allylic amine analogue was produced as the major product relative to the hydroazidation reaction. Enantiodivergence in synthetic protocols has previously been reported,[23] and is usually brought about by modification of various reaction parameters, including catalyst identity (e.g. changes to metal or ligand), temperature, solvent, and additives, among others. However, the dependence of product stereochemistry on the identity of nucleophile is relatively rare.[24,25]

On the basis of this discovery, we pursued efforts to optimize the hydroamination reaction with the *tert*-butyl carbamate nucleophile (Table 4).[26] In all cases, complete regio- and diastereoselectivity was observed. The same ADC gold(I) catalysts were surveyed (entries 1–5), and the electron-rich 3,5-dimethoxy aryl substituted ligand **A4** was found to give the best enantioselectivity (entry 4). Chlorinated and aromatic solvents were found to decrease the observed enantioselectivity (entries 6 and 7). Other ethereal solvents such as dimethoxymethane and tetrahydrofuran (entries 8 and 9) performed slightly worse than 1,4-dioxane, which was ultimately the optimal choice. Finally, increasing the equivalents of the

carbamate afforded elevated yields (entries 10 and 11), which could be improved even more by extending the reaction time to 24 hours (entry 12).

With these two sets of optimized conditions in hand, the substrate scope was investigated for both reactions (Table 4). Introduction of aromatic substituents revealed that both electron-donating and withdrawing groups were well-tolerated at various positions on the ring (entries 1–12).[27] A heterocyclic substrate also gave good yields and moderate enantioselectivities (entry 13). Notably, in some cases the yield and enantioselectivity observed in the hydroazidation reaction was markedly better than that of hydroamination (entries 4 and 10) and *vice versa* (entries 7 and 12), further illustrating the complementary of the two manifolds.

Introduction of a larger terminal alkyl substituent (*n*-propyl) proved challenging in the hydroazidation reaction and resulted in only moderate yield and enantioselectivity (Scheme 2a). However, in the case hydroamination, excellent enantioselectivity was maintained with a small decrease in yield (Scheme 2b), overcoming the requirement for a methyl-substituted allene in the previously reported allene hydroamination.[26]

In summary, we have demonstrated the first asymmetric hydroazidation of unconjugated carbon-carbon π-bonds. The use of ADC gold(I) catalysts derived from BINAM, 1,3-disubstituted allenes, and hydrazoic acid generated *in situ* allows for the enantioselective preparation of chiral allylic azide products. Additionally, we have disclosed a related protocol for hydroamination of allenes. Both classes of product compounds were synthesized with high levels of regio- and diastereoselectivities, and with moderate to high enantioselectivities (up to 92% ee). The two reaction manifolds are complementary and, therefore, allow access to a range of enantioenriched allylic amine products using the same catalyst family. Notably, a single enantiomer of the catalysts can generate allylic amines with opposite chirality.[28] Moreover, in cases where the hydroamination fails to provide allylic amines with useful enantioselectivities, the hydroazidation reaction can be used to address these deficiencies and *vice versa*. Efforts to exploit to complementary reactivity of the hydroazidation and hydroamination reactions, and to explore the origin of the reversal in enantioinduction are currently underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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19. Installation of the 3,3′-substituents on BINAM requires hydrogenation of the backbone prior to exclusive 3,3′-iodination. After iodination, the subsequent oxidation to re-aromatize the backbone is often low-yielding, and was therefore avoided. Supporting Information for details.
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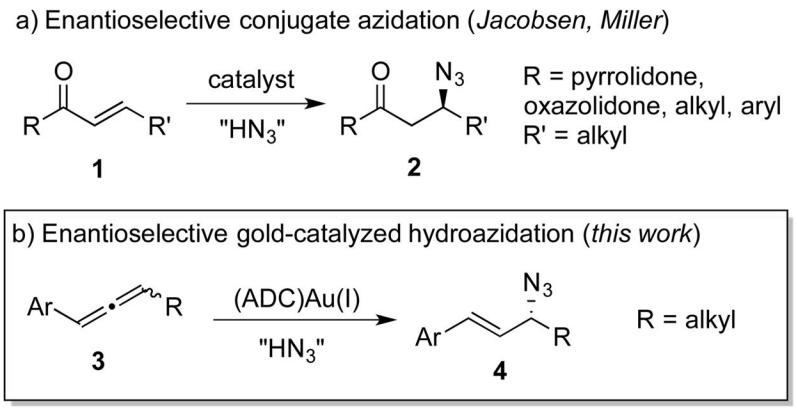
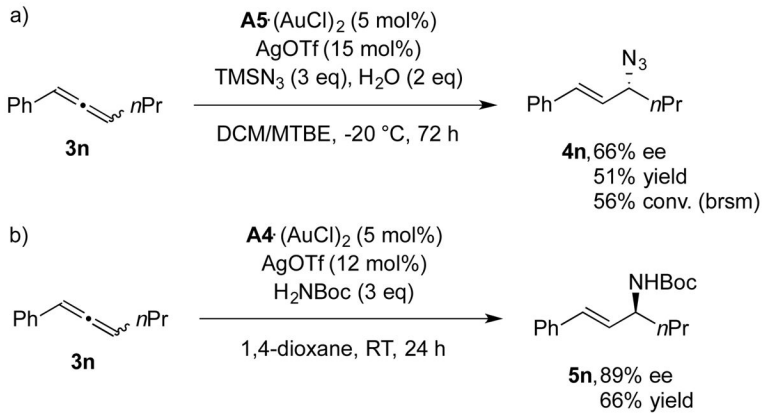
26. For the enantioselective intermolecular hydroamination of allenes with benzyl carbamate, see: Butler KL, Tragni M, Widenhoefer RA. Angew Chem Int Ed. 2012; 51:5175–5178.

27. For additional allene substrates that underwent hydroazidation, see Supporting Information.

28. Staudinger reduction and Boc-protection of 4a was carried out in the same pot to furnish (*R*)-5a without loss of enantioselectivity. Additionally, azide 4a was subjected to CuAAC with phenylacetylene, affording the corresponding triazole product with identical enantiomeric excess. See Supporting Information for details.



Scheme 1.
Enantioselective conjugate azidations and hydroazidations

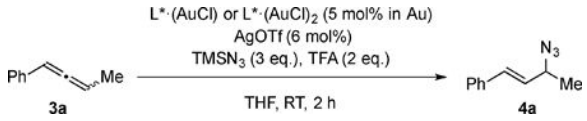


Scheme 2.

Reactions of *n*-propyl substituted allene

Table 1

Assessment of chiral gold(I) catalysts



Entry[a]	Precatalyst	Yield[b]	ee[c]
1	(*R*)-DM-SEGPHOS·$(AuCl)_2$	50	20
2	(*R*)-DTBM-BINAP·$(AuCl)_2$	49	10
3	**P1**·(AuCl)	35	2
4	**N1**·(AuCl)	21	5
5	**N2**·(AuCl)	51	3
6	**N3**·(AuCl)	12	2
7	**A1**·$(AuCl)_2$	37	60

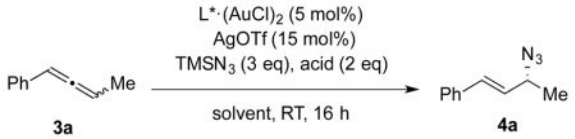
*[a]*Conditions: 0.1 mmol **3a**, 0.005 mmol precatalyst (0.0025 mmol for dinuclear gold precatalysts), 0.06 mmol AgOTf, 0.3 mmol $TMSN_3$, 0.2 mmol TFA, 1.0 mL THF (0.1 M), 2 h at room temperature.

*[b]*Determined by ^1H NMR with 1,3,5-trimethoxybenzene as an internal standard.

*[c]*Determined by chiral HPLC.

Table 2

Optimization of hydroazidation with ADC gold(I) catalysts



Entry[a]	Precatalyst	Solvent	Acid	Yield[b]	ee[c]
1	**A1**·$(AuCl)_2$	THF	TFA	24	50
2	**A2**·$(AuCl)_2$	THF	TFA	36	72
3	**A3**·$(AuCl)_2$	THF	TFA	15	46
4	**A4**·$(AuCl)_2$	THF	TFA	41	50
5	**A5**·$(AuCl)_2$	THF	TFA	45	73
6	**A5**·$(AuCl)_2$	THF	AcOH	40	71
7	**A5**·$(AuCl)_2$	THF	H_2O	77	75
8	**A5**·$(AuCl)_2$	THF/PhMe[d]	H_2O	91	73
9	**A5**·$(AuCl)_2$	THF/$CHCl_3$[d]	H_2O	91	73
10[e]	**A5**·$(AuCl)_2$	THF/$CHCl_3$[d]	H_2O	92	90[f]

[a] Conditions: 0.1 mmol **3a**, 0.005 mmol precatalyst, 0.015 mmol AgOTf, 0.3 mmol $TMSN_3$, 0.2 mmol acid, 2.0 mL of appropriate solvent (0.05 M), 16 h at room temperature.

[b] Determined by ^1H NMR with 4-chloroanisole as an internal standard.

[c] Determined by chiral HPLC.

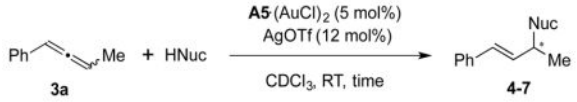
[d] 3:1 volumetric ratio.

[e] Reaction run at −10 °C for 72 hours.

[f] Isolated yield.

Table 3

Assessment of nitrogen nucleophiles



3a 4-7

Entry[a]	HNuc	Time	Product	Major enantiomer[b]	ee[c]
1	HN_3[d]	60 m	**4a**	*R*	35
2	H_2NBoc	24 h	**5a**	*S*	27
3	$H_2NNHBoc$	14 d	**6**	*S*	65
4	H_2NPh	14 d	**7**	*S*	30

[a] Conditions: 0.05 mmol **3a**, 0.0025 mmol precatalyst, 0.006 mmol AgOTf, 0.15 mmol nucleophile, 1.0 mL $CDCl_3$ (0.05 M).

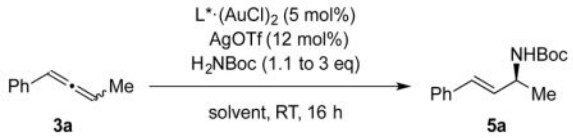
[b] Determined by optical rotation and comparison to literature precedents (see Supporting Information for details)

[c] Determined by chiral HPLC.

[d] Generated *in situ* from $TMSN_3$ (0.15 mmol) and TFA (0.10 mmol).

Table 4

Optimization of hydroazidation with ADC gold(I) catalysts



Entry[a]	Precatalyst	Solvent	Equivalents of carbamate	Yield[b]	ee[c]
1	**A1**·$(AuCl)_2$	1,4-dioxane	1.1	33	77
2	**A2**·$(AuCl)_2$	1,4-dioxane	1.1	32	79
3	**A3**·$(AuCl)_2$	1,4-dioxane	1.1	28	85
4	**A4**·$(AuCl)_2$	1,4-dioxane	1.1	53	89
5	**A5**·$(AuCl)_2$	1,4-dioxane	1.1	46	81
6	**A4**·$(AuCl)_2$	DCM	1.1	54	30
7	**A4**·$(AuCl)_2$	PhMe	1.1	73	75
8	**A4**·$(AuCl)_2$	DMM	1.1	48	84
9	**A4**·$(AuCl)_2$	THF	1.1	30	82
10	**A5**·$(AuCl)_2$	1,4-dioxane	2.0	62	89
11	**A5**·$(AuCl)_2$	1,4-dioxane	3.0	64	89
12[d]	**A5**·$(AuCl)_2$	1,4-dioxane	3.0	89[e]	89

[a] Conditions: 0.05 mmol **3a**, 0.0025 mmol precatalyst, 0.006 mmol AgOTf, 0.15 mmol H_2NBoc, 1.0 mL of appropriate solvent (0.05 M), 16 h at room temperature.

[b] Determined by 1H NMR with 1,3,5-trimethoxybenzene as an internal standard. The mass balance is unconsumed starting material and traces of the hydration product.

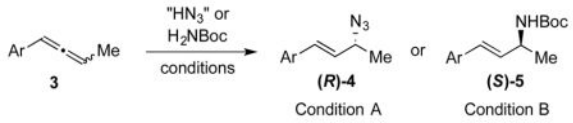
[c] Determined by chiral HPLC.

[d] Reaction run for 24 hours.

[e] Isolated yield.

Table 5

Substrate Scope of hydroazidation and hydroamination



Entry[a],[b]	3	Ar	4, yield[c], ee[d]	5, yield[c], ee[d]
1	**3a**	Ph	**4a**, 92, 90	**5a**, 89, 89
2	**3b**	4-MeC_6H_4	**4b**, 89, 84	**5b**, 82, 80
3	**3c**	4-Si$Me_3C_6H_4$	**4c**, 67, 74	**5c**, 56, 73
4	**3d**	4-PhC_6H_4	**4d**, 84, 84	**5d**, 49, 64
5	**3e**	4-FC_6H_4	**4e**, 86, 86	**5e**, 75, 87
6	**3f**	4-BrC_6H_4	**4f**, 88, 90	**5f**, 84, 92
7	**3g**	4-$CF_3C_6H_4$	**4g**, 41, 74	**5g**, 97, 92
8	**3h**	3-MeC_6H_4	**4h**, 89, 85	**5h**, 63, 83
9	**3i**	3-OMeC_6H_4	**4i**, 65, 84	**5i**, 82, 78
10	**3j**	3-PhC_6H_4	**4j**, 92, 89	**5j**, 74, 72
11	**3k**	3-BrC_6H_4	**4k**, 87, 88	**5k**, 77, 85
12	**3l**	2-MeC_6H_4	**4l**, 81, 62	**5l**, 74, 80
13	**3m**	3-thienyl	**4m**, 86, 75	**5m**, 71, 77

*[a]*Condition A: 0.1 mmol **3**, 0.005 mmol **A5**·$(AuCl)_2$, 0.015 mmol AgOTf, 0.3 mmol $TMSN_3$, 0.2 mmol H_2O, in 2.0 mL of THF:$CHCl_3$ (3:1 v/v, 0.05M), 72 h at −10 °C. Condition B: 0.05 mmol **3**, 0.0025 mmol **A4**·$(AuCl)_2$, 0.006 mmol AgOTf, 0.15 mmol *tert*-butyl carbamate, in 1.0 mL of 1,4-dioxane (0.05M), 24 h at rt.

*[b]*Absolute stereochemistry assigned by analogy to **4a** and **5a**.

*[c]*Isolated yield.

*[d]*Determined by chiral HPLC.